Recognition of Adverse Reactions following Smallpox Vaccination

Department of Health and Human Services
Centers for Disease Control and Prevention
January 22, 2003

Recognition of Adverse Reactions following Smallpox Vaccination

- Learning Objectives:
  - Describe the common and serious adverse reactions expected after smallpox vaccination
  - Describe the treatment options available to treat a person with an adverse reaction following smallpox vaccination

Adverse Event vs. Adverse Reaction

- **Adverse reaction:** untoward effect extraneous to the vaccine's primary purpose of producing immunity
  - shown to be caused by the immunization
  - aka vaccine side effects or complications

- **Adverse event:** untoward effects observed or reported following immunizations, but a causal relationship between the two have yet to be established.

Expected Reactions following vaccination

- Fatigue, headache, myalgia, regional lymphadenopathy, and lymphangitis
- Pruritus, swelling, and erythema at vaccination site
- Satellite lesions are benign findings and require no therapy
- Fever

Fever in Children

- Historically first-time vaccination in children:
  - >100F for >1 day on day 4-14 following vaccination (70%)
  - >102F (15-20%)

Fever in Adults

- Less common in adults than children
- When fever occurs in adults it is more frequently noted in first-time vaccinees than revaccinees

Smallpox Vaccine Reactions: NIH Dilutional Trial Experience in First-time vaccinees* (n=680)

Symptoms occurring within two weeks post-vaccination

- Fatigue (50%), headache (40%), muscle aches and chills (20%), nausea (20%)
- Fever ≥ 100F (10%)
- Pain at site (86%)
- Regional lymphadenopathy (54%)
- Sufficiently ill (30%)
  - Trouble sleeping
  - Missed school, work or recreational activities

*Frey et al NEJM 2002 346(17)1265-74

CDC Diary Card Database unpublished, 2002

- Similar findings regarding type and frequency of symptoms (n~600)
- Majority reported symptoms (not including pruritus) on post-vaccination days 3-7 (78%)
- Both NIH and CDC: majority of symptoms were self limited and required only symptomatic care

Smallpox Vaccine Adverse Reactions

- Nonspecific dermatological conditions
- Inadvertent inoculation
- Ocular vaccinia
- Generalized vaccinia
- Eczema vaccinatum
- Progressive vaccinia (vaccinia necrosum)
- Post-vaccinial encephalitis
- Fetal vaccinia
- Other
- Not yet characterized

Major Complications of Smallpox Vaccination

- Definitive studies of complications of smallpox vaccination by Lane et al, published in 1969-1970

- Led to the recommendation to cease routine smallpox vaccination in the United States

Smallpox Vaccine Adverse Reaction Rates*

Reaction	Primary Vaccination
Inadvertent inoculation	25-529
Generalized vaccinia	23-242
Eczema vaccinatum	10-39
Progressive vaccinia	0.9-1.5
Post-vaccinial encephalitis	3-12
Death	1

*Rates per million primary vaccinations.
Source: Lane 1968 National and State Surveys

Adverse Reactions in Contacts

- Close contact, relaxed infection control usually occurring in the home
- Nosocomial infection(s) reported
- Same risk factors
- Reports of Inadverent inoculation, eczema vaccinatum and fetal vaccinia
- Contacts with eczema or atopic dermatitis have more severe EV and worse outcome

Smallpox Vaccine Adverse Deaths (1959-1966 and 1968)*

Adverse Reaction(s)	Deaths (%)
Central Nervous System disease	36 (52%)
Progressive vaccinia	19 (28%)
Eczema vaccinatum	12 (18%)
	Total N=68 deaths

*Source: Lane et al. Deaths attributable to smallpox vaccination. JAMA 1970;212

Smallpox Vaccine Adverse Reactions

- Adverse reaction rates may be higher today than in 1960s
- More persons at risk because of higher prevalence of immunosuppression and eczema/atopic dermatitis
- Adverse reaction rates lower among previously vaccinated persons
- Limit occurrence of adverse reactions with appropriate screening

Laboratory Diagnostics

- Adverse reactions most often diagnosed by clinical evaluation and history
- Diagnostic testing usually done to rule out other conditions (e.g., varicella, herpes simplex)
- Serologic testing for vaccinia usually not helpful in majority of cases without baseline values

Treatment of Adverse Reactions

- Under Investigational New Drug Protocol(s):
  - Vaccinia immune globulin (VIG)
  - Cidofovir (second line)
- Available from CDC and DoD
- For use in select adverse events

Vaccinia Immune Globulin (VIG)

- Immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine
- Effective for treatment of eczema vaccinatum, progressive vaccinia, generalized vaccinia (severe form), and select cases of ocular vaccinia
- Not effective in post-vaccinial encephalitis

Cidofovir

- Antiviral
- Activity against Orthopoxviruses in vitro and animal models
- Currently approved for treatment of CMV retinitis in persons with AIDS

Nonspecific Rashes

- Flat, erythematous, macules or patches, and generalized urticarial rashes
- Usually do not become vesicular
- Onset ~ 10 days post-vaccination
- Afebrile patient, well appearing
- Spontaneously resolves ~2-4 days
- Immune response vs. viral replication
- Antipruritics

Nonspecific rash following smallpox vaccination

Photo credit: J. Michael Lane, MD MPH
CDC Teaching slide set
Adverse reactions following smallpox vaccination

Nonspecific rash following smallpox vaccination

Photo credit: Vaccination reactions in vaccinia-naive volunteers in a clinical study of diluted Dryvax® enrolled in NIAID VTEUs

Erythema Multiforme

- Variety of lesions include macules, papules, urticaria, and typical bulls-eye (targetoid) lesions
  - Central, dark papule, surrounded by pale zone and a halo of erythema
- Course is extrapolated from other infectious agents (HSV, mycoplasma)
- ~10 days after vaccination
- Occasional Stevens-Johnson syndrome
  - >2 mucosal surfaces / 10% BSA

ERYTHEMA MULTIFORME

Photo credit: V. Fulginiti, MD and Logical Images

http://www.bt.cdc.gov/training/smallpoxvaccine/reactions/default.htm

EM and SJS

- Hypersensitivity reactions
- Lesions are not thought to contain virus
- Antipruritics
- VIG not indicated
- Supportive care (hospitalize for SJS)
- Role of steroids in SJS controversial
  - Consult immunologist, dermatologist, or infectious disease specialist

Stevens-Johnson Syndrome

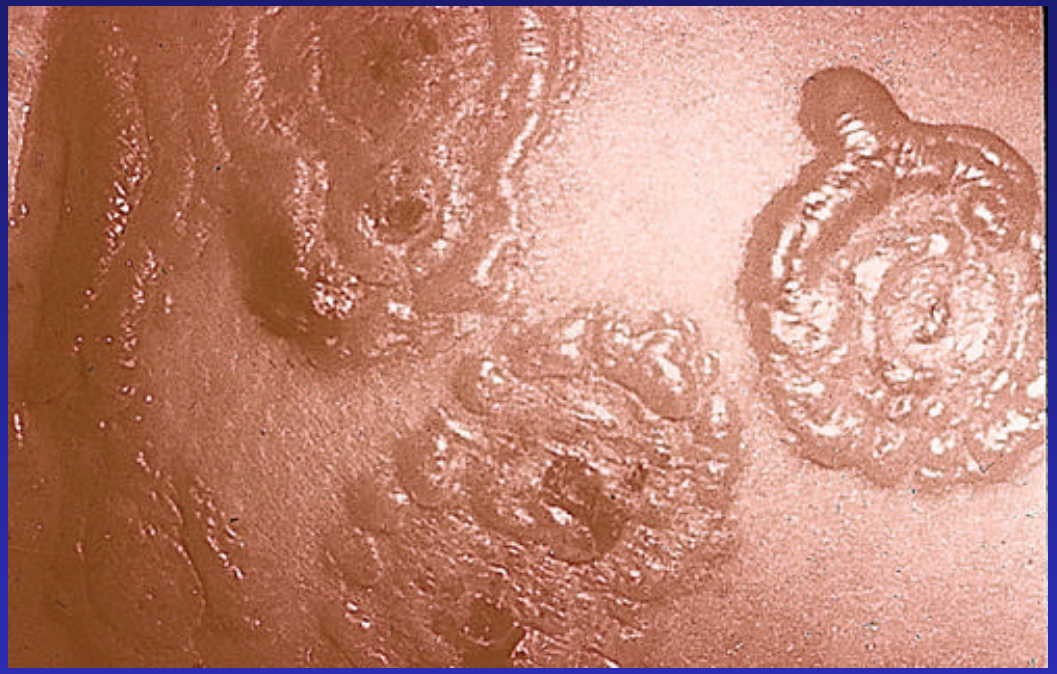

Photo credit: J. Michael Lane, MD MPH
CDC Teaching slide set
Adverse reactions following smallpox vaccination

Inadvertent Inoculation

- Transfer of vaccinia virus from vaccination site to another site on the body, or to a close contact
- Most frequent complication of smallpox vaccination
- Most common sites are periocular/ocular, face, nose, mouth, genitalia, rectum
- Lesions contain vaccinia virus and follow vaccination course

Inadvertent inoculation

Photo credit: J. Michael Lane, MD MPH
CDC Teaching slide set
Adverse reactions following smallpox vaccination

Inadvertent inoculation
Multiple sites in young children

Photo credit: V. Fulginiti, MD and Logical Images
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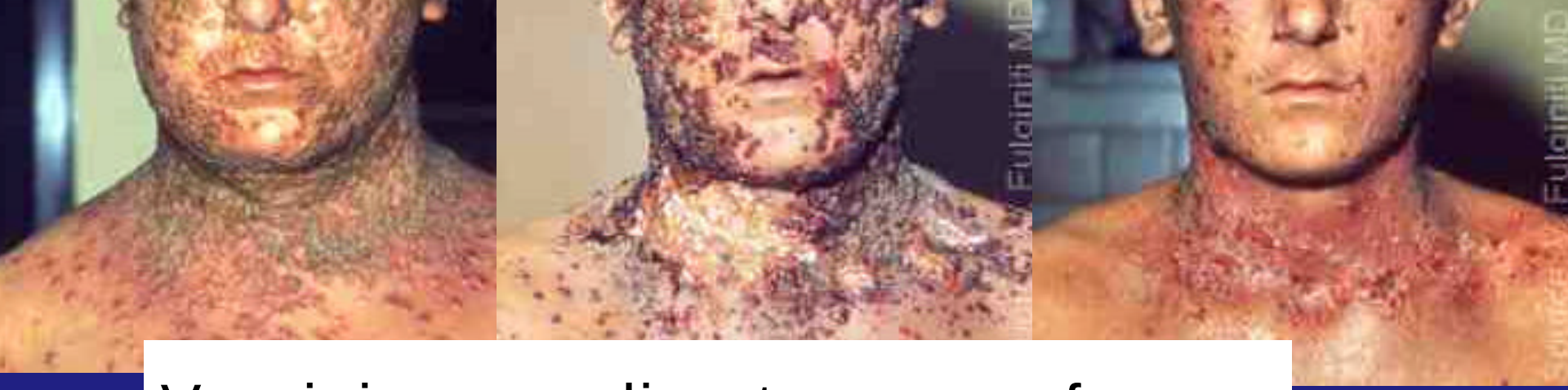
Inadvertent Inoculation

- Hand washing after contact with vaccination site or contaminated material most effective prevention
- Uncomplicated lesions require no therapy, self-limited, resolve in ~3 weeks
  - Risk factors: disruption of epidermis or very young
- VIG may speed recovery if extensive or severe manifestation (e.g., significant pain)



Vaccinia spreading to areas of acne

Diaper area

Implantation from scratching

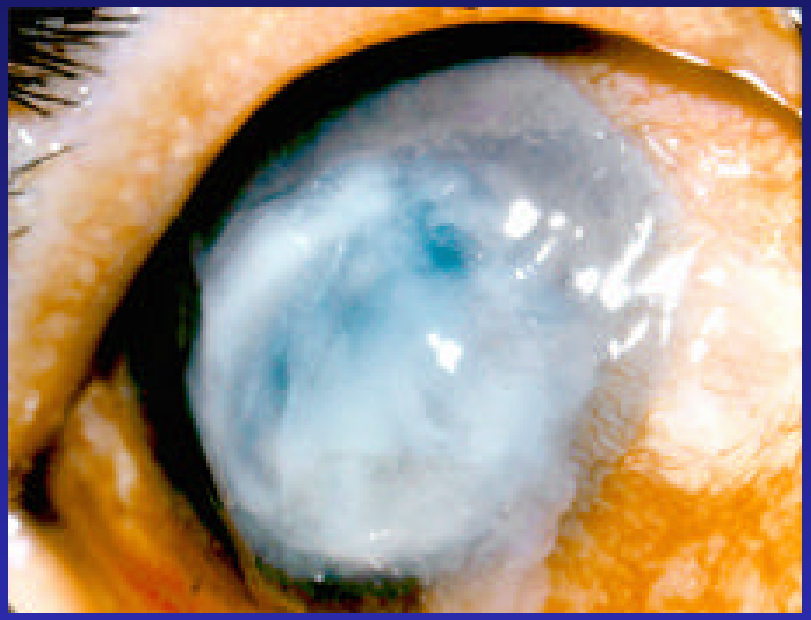
Photo credit: V. Fulginiti, MD and Logical Images

http://www.bt.cdc.gov/training/smallpoxvaccine/reactions/default.htm

Inadvertent inoculation resulting in ocular vaccinia infection

Ocular Vaccinia

- May present as blepharitis, conjunctivitis, keratitis, iritis, or combination
- Should be managed in consultation with an ophthalmologist
- Treatment may include topical ophthalmic topical antiviral agents, topical steroids and topical antibacterials and VIG



Ocular vaccinia

Photo credit: D. Pavan-Langston in AJO, unpublished 2003

Generalized Vaccinia

- Vesicles or pustules appearing on normal skin distant from the vaccination site
- Usually occur 6-9 days after vaccination
- Anywhere on body; Few or numerous lesions
- Regional form (extensive satellite vesiculation)
- Can be confused with EM when there is significant erythema
- Often accompanied by fever, headache, and myalgias

Photo credit: J. Michael Lane, MD MPH
CDC Teaching slide set
Adverse reactions following smallpox vaccination

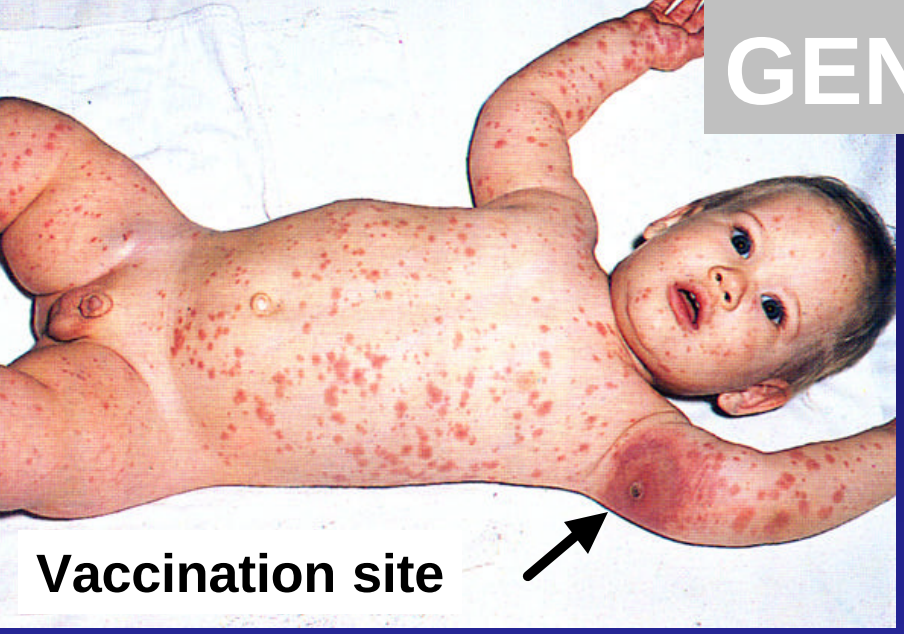
Generalized Vaccinia

- Differential diagnosis
  - Erythema multiforme
  - Eczema vaccinatum
  - Inadvertent inoculation at multiple sites
  - Early progressive vaccinia
  - Disseminated herpes
  - Severe varicella

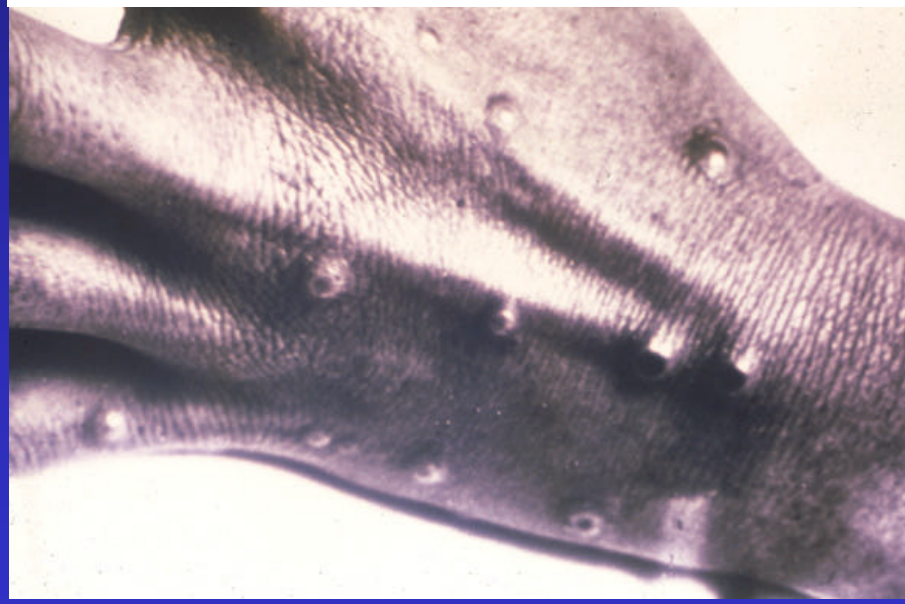
Generalized Vaccinia

- Generally self-limited in immunocompetent hosts
- Most cases do not require therapy
- VIG may be considered for severe disease or underlying illness
- Thought to be due to viremia
- Lesions contain vaccinia use infection control precautions

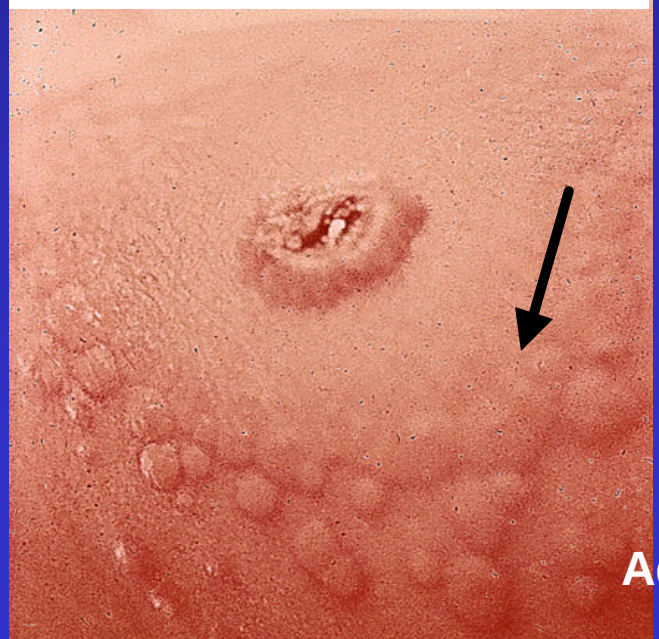
GENERALIZED VACCINIA



Sometimes resembles Smallpox



Regional form



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Adverse reactions following smallpox vaccination

Generalized vaccinia – varying presentatio

Photo credit: V. Fulginiti, MD and Logical Images

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Eczema Vaccinatum

- Localized or generalized papular, vesicular or pustular rash
- Onset concurrent or shortly after vaccinial lesion at vaccination site
- Lesions follow same course as vaccination site, may be confluent with/without umbilication
- Fever, lymphadenopathy and systemically ill

Eczema Vaccinatum in 3yo contact
Lesions resemble normal vaccination site

Photo credit: J. Michael Lane, MD MPH
CDC Teaching slide set
Adverse reactions following smallpox vaccination

Eczema Vaccinatum in Contact Outcome: death

Photo credit: J. Michael Lane, MD MPH
CDC Teaching slide set
Adverse reactions following smallpox vaccination

Eczema Vaccinatum

- Predilection for site of atopic dermatitis (eczema) eruptions
- Severity independent of the activity of the underlying eczema
- In contacts onset ~5-19 days following suspected exposure
- Severe cases among contacts of recently vaccinated person

Confluence and Umbilication
days post-vaccination

3 days later
VIG started
Edema, crusting

3 days after VIG
14 days post-vaccinat
Resolution, pit and s

Progression of EV in first-time vaccinee treated with VIG

Photo credit: J. Michael Lane, MD MPH

Eczema vaccinatum in a contact

Photo credit: J. Michael Lane, MD MPH
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Eczema vaccinatum in a contact

Photo credit: J. Michael Lane, MD MPH
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Eczema vaccinatum in a contact with residual scarring

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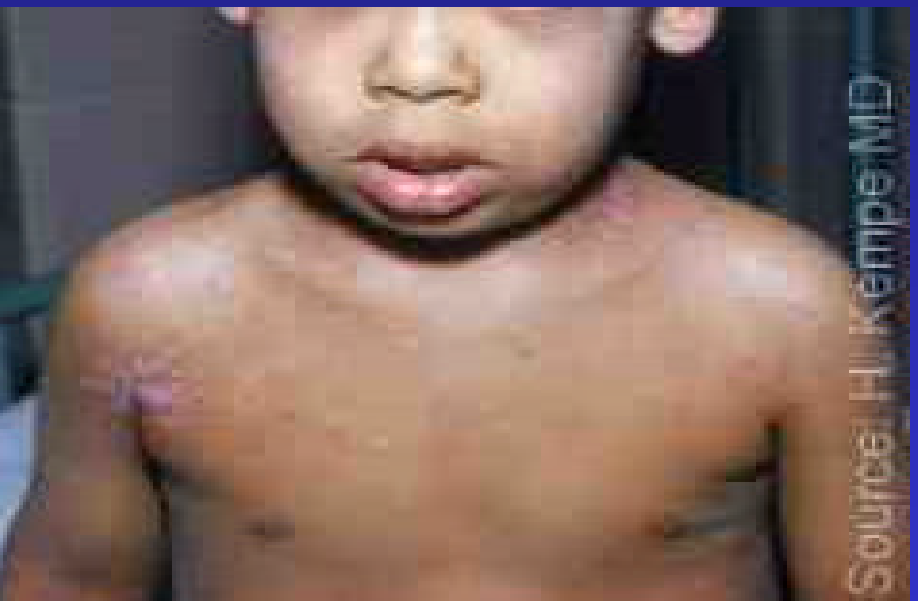
EV predilection for sites of atopic dermatitis (eczema)



Healed EV

Multiple umbilicated EV papular lesions

Photo credit: V. Fulginiti, MD, H. Kempe MD and Logical Images
http://www.bt.cdc.gov/training/smallpoxvaccine/reactions/default.ht

Eczema Vaccinatum

- Management
  - Hemodynamic support
  - Meticulous skin care
  - Early treatment with VIG
  - Treatment of secondary bacterial or fungal infections as needed
- Lesions contain vaccinia virus: infection control precautions

Progressive Vaccinia

- Rapid, progressive and painless extension of central vaccination lesion OR progression without apparent healing after 15 days
- Virus continues to spread locally and through viremia (metastatic lesions to skin, viscera and bone)
- Initially little or no inflammation at the site and generally little pain
- Bacterial superinfection may develop later

Progressive Vaccinia

- Occurs almost exclusively among persons with cellular immunodeficiency
- Can occur in persons with humoral immunodeficiency
- Can occur following revaccination of people who have become immunosuppressed since their primary vaccination

Progressive Vaccinia: Prognosis

- Protective T-cell count level and humoral immunity unknown although anecdotal reports of poorer prognosis with CMI deficits
- Better prognosis if immunosuppression is reversible (e.g. systemic steroid use)

Atypical PV in 64yo with lymphoma and IgA, IgM and IgA deficiency

Photo credit: J. Michael Lane, MD MPH
CDC Teaching slide set Adverse reactions

Progressive Vaccinia vs. Severe Take

- Distinguishing features of severe take:
  - Resolves in 1-2 weeks w/o therapy
  - Has signs and symptoms of inflammatory response
  - Pain is present
  - Lesion does not rapidly extend
  - Absence of metastatic lesions
  - Occurs in immunocompetent host

PV: Differential Diagnosis

- Ulcerative take
- Severe bacterial infection
- Severe chickenpox
- Disseminated herpes simples
- Other necrotic conditions

Progressive vaccinia with metastatic lesions in adult with CLL

Photo credit: J. Michael Lane, MD MPH
CDC Teaching slide set Adverse reactions

SCID

Lymphoma and PV

Lymphosarcoma

Hypogammaglobulinemia

Progressive vaccinia

Photo credit: V. Fulginiti, MD and Logical Images

Child with absent

cell-mediated immune function

Progressive vaccinia

Photo credit: V. Fulginiti, MD and Logical Images

http://www.bt.cdc.gov/training/smallpoxvaccine/reactions/default.htm

Progressive Vaccinia

- Requires aggressive therapy with VIG
- Newer antivirals not studied in humans. Cidofovir second-line agent
- Surgical debridement used in past with variable success
- Anticipate high mortality rate despite modern advances in medical care
- Lesions contain vaccinia virus: Infection control precautions

Central Nervous System Disease post-vaccination

- Usually affects primary vaccinees <12 months of age and adolescents and adults receiving a primary vaccination
- Presents with any of a variety of CNS signs (e.g., ataxia, confusion, paralysis, seizures, or coma)
- 15%-25% die, 25% develop neurological sequelae

Post-vaccinial encephalitis (PVE) and post-vaccinial encephalomyelitis (PVEM)

- PVE - <2 years of age
  - 6-10 days post-vaccination
  - Cerebral vascular changes
- PVEM - >2 years of age
  - 11-15 days post-vaccination
  - Demyelinating changes

PVEM and PVE: Diagnosis and evaluation

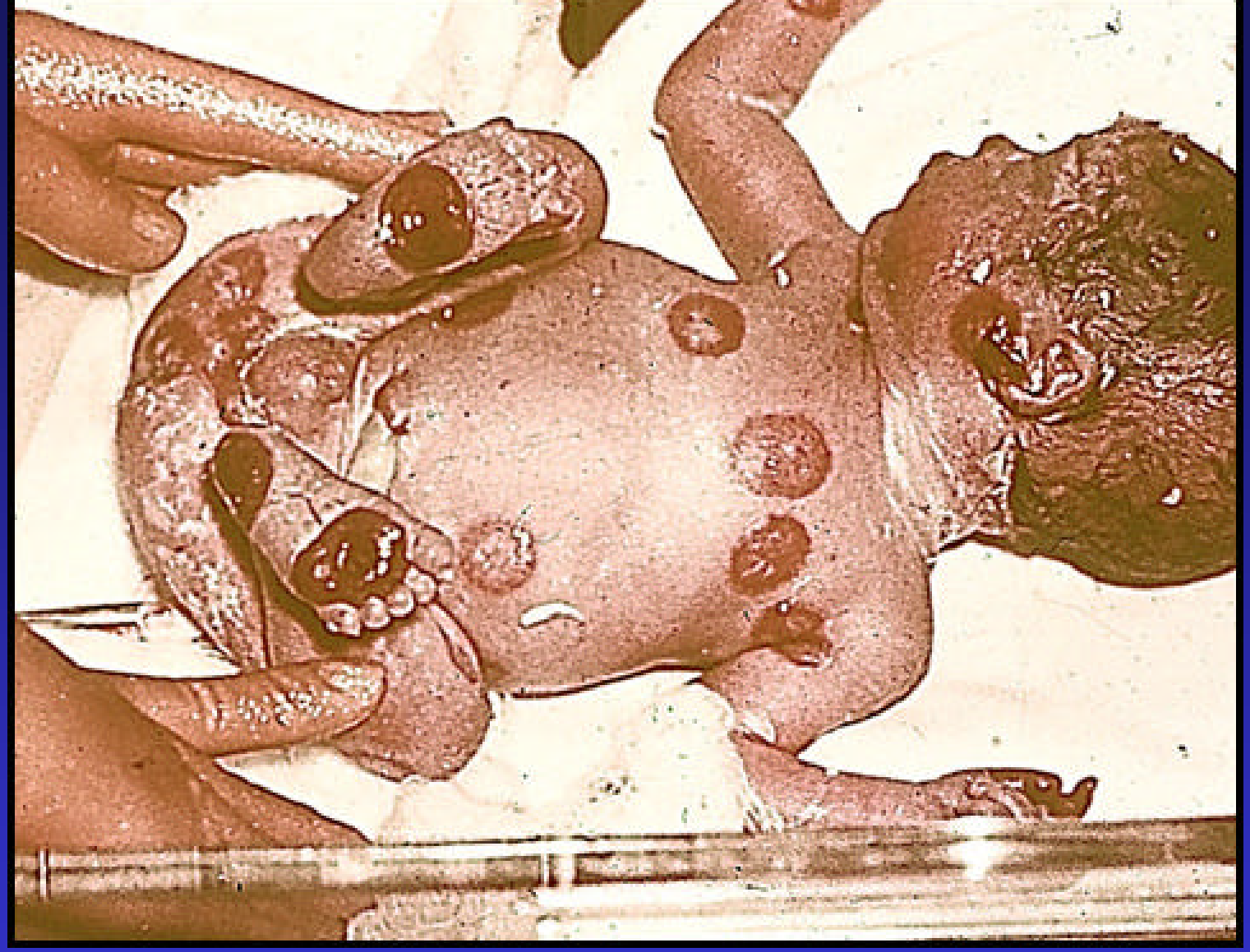
- Diagnosis of exclusion
- Other infectious or toxic causes of encephalitis should be ruled out
- Pathophysiology not well understood but thought to be immune response
- CSF findings normal or nonspecific
- Use of modern imaging studies has not been evaluated

PVE and PVEM: Treatment

- Treatment is supportive
- VIG not effective
- Anticonvulsive therapy and intensive care may be required

Fetal Vaccinia

- Disseminated viremia with characteristic lesions
- Rare complication (<50 cases reported)
- Cases reported in association with all trimesters, but greatest risk appears to be 3rd trimester
- Outcomes: premature birth, fetal loss, high mortality
- No known pattern of congenital malformations



FETAL VACCINIA

Photo credit: J. Michael Lane, MD MPH
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Fetal Vaccinia

- Death usually occurs before birth or in perinatal period
- Route of transmission unknown
- VIG may be considered if infant born alive with lesions
- Antivirals not recommended
- No known reliable intrauterine diagnostic test

Fetal vaccinia

Photo credit: J. Michael Lane, MD MPH
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following smallpox vaccination

Other reported adverse reactions

- Cardiac: pericarditis, myocarditis
- Neurological: TM, seizures, paralysis
- Osteomyelitis (virus recovered)
- Skin changes at the vaccination scar: Malignancy, discoid lupus and Graves myedema
- Erythema nodosum leprosum or neuritis in leprosy patients

For More Information

- CDC Smallpox website
  www.cdc.gov/smallpox
- National Immunization Program website
  www.cdc.gov/nip
- Clinical Evaluation Tools
  www.bt.cdc.gov/agent/smallpox/vaccination/clineval
- CDC Clinician Information Line
  1-877-554-4625

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